AHRQ Comparative Effectiveness Review Surveillance Program

CER # 37:
Chronic Kidney Disease Stages 1–3: Screening, Monitoring, and Treatment

Original release date:
January 2012

Surveillance Report:
October 2012

Key Findings:

- The conclusions for KQ2 (harms of screening) and KQ4 (harms of monitoring), KQ6 (harms of treatment) are still considered valid
- The conclusions for KQ1 (benefits of screening), KQ3 (benefits of monitoring), KQ5 (benefits of treatment) are still considered valid but additional studies are available
- For KQ5 (benefits of treatment) and KQ6 (harms of treatment) there were several adverse events that should be followed up.

Summary Decision

This CER's priority for updating is **Low**

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project:

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Contents

Chronic Kidney Disease Stages 1–3: Screening, Monitoring, and Treatment

1. Introduction

Comparative Effectiveness Review (CER) #37, Chronic Kidney Disease Stages 1–3: Screening, Monitoring, and Treatment was released in January 2012.[1] It was therefore due for a surveillance assessment in July 2012.

2. Methods

2.1 Literature Searches

Using the search strategy employed for January, 2011-August 7, 2012. The search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (Kidney International, American Journal of Kidney Diseases, Diabetes Care, Archives of Internal Medicine, and the Journal of American Society of Nephrology). The specialty journals were those most highly represented among the references for the original report. This search resulted in 81 titles to review. Appendix A includes the search strategy.

2.2 Study selection

In general we used the same inclusion and exclusion criteria as the original CER.

2.3 Expert Opinion

We shared the conclusions of the original report with 10 experts in the field (including the original project leader, suggested field experts, original technical expert panel (TEP) members, and peer reviewers) for their assessment of the need to update the report and their recommendations of any relevant new studies; the project leader and six subject matter experts completed the questionnaire matrix. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa Method and/or the RAND Method suggesting the need for an update. The criteria are listed in the table below.[2, 3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any FDA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that

might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The literature search identified 81 titles. After title and abstract review, we further reviewed the full text of 29 journal articles. The remaining 52 titles were rejected because they were editorials, letters, or did not include topics of interest. Eleven further articles were reviewed at the suggestion of the experts.

Through literature searches and expert recommendations, 40 articles went on to full text review. Of these, 20 were rejected because they were non-systematic reviews, did not include a comparison of interest, or did not address the key questions. Thus, 20 articles were abstracted into an evidence table (Appendix B).[4-23]

3.2 Expert Opinion

All 6 experts were in agreement that the conclusions are up-to-date.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the

Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signal.

Table 1. Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
CKD Treatment Benefits and Harms				
In RCTs of patients with CKD Stages 1-3 several treatments reduced the risk of clinical outcomes, but the benefits appeared to be limited to specific CKD subgroups, some of which already had a clinical indication for the treatment studied (Table A).	No new studies were identified	None relevant	All 6 experts thought this conclusion was still valid. However, 1 noted that the word 'but' appears to limit the importance of this finding, even though the specific subgroups are large (type 1 and type 2 diabetics).	The conclusion is still valid
ACEI and/or ARB treatment significantly reduced ESRD risk in patients with proteinuria (macroalbuminuria), most of whom had diabetes and hypertension. ESRD was not significantly reduced in patients with CKD stages 1–3 who did not have proteinuria. Patients with proteinuria, diabetes, and hypertension may benefit from ACEI or ARB treatment.	There was one study that furthered this examination of ESRD by looking at a subset of 1414 Black patients in the Accomplish trial.[23] They were followed for 3 years and found doubling in serum creatinine, ESRD or death was not different between Black and non-Black patients, although Blacks have modestly higher increased risk for more advanced increases in serum Cr than non-Blacks	There were 5 significant issues related to ACEI and/or ARB treatment. Benazepril- erythema multiforme including Steven-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis. Perindopril- hepatic failure. Valsartan- hemolytic anemia. Captopril- co-administration with NSAIDs may result in deterioration of renal function including possible ARF, especially in elderly, volume-depleted, or with compromised renal function. Both ACEI and ARB- neonatal hypotension	5 experts thought this conclusion was still valid. 1 was not sure.	The conclusion is still valid but an additional study is available and the adverse event signals should be followed up

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
ACEI treatment significantly reduced mortality risk in patients known to have microalbuminuria who had either cardiovascular disease or the combination of diabetes and other cardiovascular risk factors. Relative risk reduction was not significantly different than in similar patients who did not have microalbuminuria. Patients who had microalbuminuria and were at high risk for cardiovascular complications may benefit from ACEI treatment at adequate doses.	No new studies were identified	Same as above	All 6 experts thought this conclusion was still valid. One expert added that ACEI and/or ARB treatment significantly reduced ESRD risk in patients with proteinuria (macroalbuminuria), most of whom had diabetes and hypertension. ESRD was not significantly reduced in patients with CKD stages 1–3 who did not have proteinuria. Patients with proteinuria, diabetes, and hypertension may benefit from ACEI or ARB treatment. Another expert recommendd seeing new KDIGO guideline on BP in CKD.	The conclusion is still valid with additional information from the experts

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Statins significantly reduced the risk of mortality, myocardial infarction (MI), and stroke in patients with hyperlipidemia and impaired eGFR or creatinine clearance, including those without coronary artery disease. Patients with hyperlipidemia and no coronary artery disease may not otherwise have an indication for statins, but the subset with CKD may benefit from treatment. No statin trials reported clinical outcomes data for patients with albuminuria.	No new studies were identified	There were 5 important warnings regarding statins: atorvastatin, fluvastatin- hepatic failure, rosuvastatin- cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria, also hepatic failure, simvastatin- dose limited to 20mg when co-administered with amiodarone, amlodipine, ranolazing due to myopathy risk; 80mg should not be started	5 experts thought this conclusion was still valid. 1 was not sure.	The conclusion is still valid. Adverse event signals should be followed up

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Beta blockers significantly reduced the risk of mortality, MI, and congestive heart failure (CHF) events in patients with CHF and impaired eGFR, most of whom already were treated with an ACEI or ARB. Patients with systolic CHF already have an indication for beta blockers, regardless of whether they have CKD.	No new studies were identified	There was a label change of Metoprolol, to include the risk of agranulocytosis, nonTCpurpura and TCpurpura	5 experts thought this conclusion was still valid. 1 expert was not sure	The conclusion is still valid. Adverse event signals should be followed up
In RCTs that compared different active treatments head to head (e.g., ACEI versus ARB, ACEI versus beta blocker), there was no consistent significant difference in clinical outcomes between treatments, with strength of evidence ranging between low and insufficient for different comparisons.	No new studies were identified	None relevant	5 experts thought this conclusion was still valid. 1 was not sure.	The conclusion is still valid

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
In RCTs that compared high- versus low-dose treatment (ARB, statin), strict versus standard control (blood pressure, glycemia), combination versus monotherapy, and intensive multidisciplinary interventions (simultaneous targeting of blood pressure, diabetes, cholesterol, and/or reducing nephrotoxic drug exposure) versus usual care, there was no consistent significant difference in clinical outcomes between treatments, with strength of evidence ranging between low and insufficient for different comparisons.	No new studies were identified	None relevant	5 experts thought this conclusion was still valid. 1 was not sure.	The conclusion is still valid

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Low-protein diets did not significantly reduce risk of mortality, ESRD, or any clinical vascular outcome compared with usual protein diets; risk for a composite renal outcome was significantly reduced in one trial, but this study also included participants with CKD stages 4–5.	No new studies were identified, however, there was one study of sodium restriction[20] in 52 patients with non-diabetic nephropathy. There was a greater reduction of proteinuria by the addition of a low sodium diet plus an ARB. However, addition of low sodium diet alone was greater than an ARB alone. There was also a study of low-AGE diets[8] of 11 overweight and obese individuals that found that urinary albumin/ creatinine ratios were significantly better following the low AGE dietary period in obese individuals (low v high AGE diet: P=0.02). Another study[7] compared alkali-inducing fruits and vegetables to oral sodium bicarbonate and found comparable decrease in kidney injury, compared to controls, in 27 patients with stage 2 hypertensive nephropathy.	None relevant	All 6 experts thought this conclusion was still valid	The conclusion is still valid

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Although limitations in reporting impeded the quantitative synthesis of withdrawal and adverse events data from different studies, adverse events reported generally were consistent with known potential adverse effects of these treatments (e.g., hypotension with antihypertensives; cough with ACEIs; edema with calcium channel blockers; hyperkalemia with ACEIs, ARBs, and aldosterone).	No new studies were identified	There were 44 FDA alerts regarding treatments used in CKD. These AE's are for use of these medications in general, not specific to use in CKD. The great majority were for minor AE's. The most serious are listed elsewhere in this table. In addition, ezetimibe had a label change to include renal impairment per the SHARP trial and erythema multiforme when used with simvastatin. Hydrochlorothiazide- can cause an idiosyncratic acute transient myopia and acute angle-closure glaucoma. Rosiglitazone- The UK commission on Human medicines concluded that the benefits of rosiglitazone no longer outweigh its risks.	All 6 experts thought this conclusion was still valid	The conclusion is still valid but the adverse event signals should be followed up.
CKD Screening Benefits and Harms				

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
We found no direct RCT evidence that addressed whether systematic screening of adults for CKD improves clinical outcomes or increases harms.	No new studies were identified	None relevant	5 experts thought this conclusion was still valid. 1 expert was not sure.	The conclusion is still valid
Results from studies not directly linking systematic CKD screening to clinical outcomes contributed indirect evidence regarding whether CKD screening improves clinical outcomes.	No new studies were identified	None relevant	All 6 experts thought this conclusion was still valid	The conclusion is still valid

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Microalbuminuria and eGFR are sensitive screening tests for detecting one-time kidney abnormalities that may reflect CKD, but false positive rates are substantial, particularly for microalbuminuria; their sensitivity and specificity for CKD as defined by kidney dysfunction or damage lasting 3 months or longer is unknown.	No new studies were identified	None relevant	All 6 experts thought this conclusion was still valid. 1 expert cited data on 3 year persistence of eGFR.[22]	The conclusion is still valid

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Most patients with CKD stages 1–3 are clinically unrecognized. Because even populations with a high CKD prevalence (e.g., diabetes, hypertension, cardiovascular disease, older age) are not routinely tested for CKD, especially for albuminuria, systematic screening likely would lead to a large increase in CKD diagnoses.	No new studies were identified	None relevant	All 6 experts thought this conclusion was still valid. 1 expert cited a case series of low CKD awareness among those with clinical markers of kidney dysfunction. [7]	The conclusion is still valid
Because of the above-noted treatment benefits in patients who have cardiovascular disease or diabetes combined with other cardiovascular risk factors (e.g., hypertension) and are known to have albuminuria, screening such patients for microalbuminuria or macroalbuminuria could lead to early initiation of ACEI or ARB treatment and reduced risk of mortality or ESRD.	No new studies were identified	None relevant	All 6 experts thought this conclusion was still valid	The conclusion is still valid

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Because of the above-noted treatment benefits in patients who have hyperlipidemia without cardiovascular disease and are known to have impaired eGFR or creatinine clearance, screening such patients for impaired eGFR could lead to early initiation of statin treatment and reduced risk of mortality, MI, or stroke.	No new studies were identified	None relevant	All 6 experts thought this conclusion was still valid	The conclusion is still valid
Virtually no RCTs of CKD treatments identified participants through screening, so the generalizability of treatment RCT results to patients with CKD stages 1–3 identified through screening is unknown.	No new studies were identified	None relevant	All 6 experts thought this conclusion was still valid	The conclusion is still valid
We found insufficient strength of evidence addressing potential harms associated with systematic CKD screening.	No new studies were identified	None relevant	All 6 experts thought this conclusion was still valid	The conclusion is still valid
CKD Monitoring Benefits and Harms				

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
We found no direct RCT evidence regarding whether systematic monitoring of adults with CKD stages 1–3 for worsening kidney function or damage improves clinical outcomes.	No new studies were identified, however, one cohort study of the association of eGFR, proteinuria and adverse clinical outcomes found that the risks of mortality, MI and progression to kidney failure with a given level of eGFR are independently increased in patients with higher levels of proteinuria	None relevant	All 6 experts thought this conclusion was still valid	The conclusion is still valid but an additional study is available
Results from studies not directly linking systematic CKD monitoring to clinical outcomes contributed indirect evidence regarding whether CKD monitoring improves clinical outcomes.	One new Cluster-RCT of educational sessions and automated alerts for PCPs caring for patients with CKD found no difference in renal referrals or proteinuria assessments.	None relevant	All 6 experts thought this conclusion was still valid	The conclusion is still valid but an additional study is available

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Because of the above-noted treatment benefits in patients with albuminuria who have cardiovascular disease or have diabetes combined with other cardiovascular risk factors (e.g., hypertension), monitoring patients with impaired eGFR for development of albuminuria could lead to early initiation of ACEI or ARB treatment and reduced mortality or ESRD risk.	We found one retrospective longitudinal cohort[16] that adds to this a comparison of monitoring urinary albumin and urinary total protein to predict patient outcomes and found no significant difference between the two for death and doubling serum creatinine level	None relevant	All 6 experts thought this conclusion was still valid	The conclusion is still valid but an additional study is available
Because of the above-noted treatment benefits in patients with hyperlipidemia who have impaired eGFR or creatinine clearance, monitoring such patients for development of impaired eGFR could lead to early initiation of statin treatment and reduced risk of mortality, MI, or stroke.	No new studies were identified	None relevant	All 6 experts thought this conclusion was still valid	The conclusion is still valid
In patients with CKD stages 1–3, kidney function usually slowly worsens over years, but may worsen faster in selected subgroups (e.g., those with diabetes, proteinuria, hypertension, older age, obesity, or dyslipidemia).	No new studies were identified	None relevant	All 6 experts thought this conclusion was still valid	The conclusion is still valid

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
The sensitivity and specificity of eGFR and albuminuria for identifying CKD progression in patients with CKD stages 1–3 are unknown.	No new studies were identified	None relevant	5 experts thought this conclusion was still valid. 1 cited a study[21] stating separate data on CKD stage 3 with and without albuminuria would be applicable.	The conclusion is still valid but an additional study is available

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
The vast majority of patients with recognized CKD stages 1–3 have serum creatinine measured regularly, so implementation of systematic eGFR monitoring may have only a limited impact on current practice. Because only a minority of patients with CKD stages 1–3 are annually tested for albuminuria, systematic albuminuria monitoring likely would lead to an increase in patients identified with clinical worsening of CKD.	No new studies were identified	None relevant	All 6 experts thought this conclusion was still valid although 1 pointed out that this conclusion was reached through indirect evidence	The conclusion is still valid
We found insufficient strength of evidence addressing potential harms associated with systematic CKD monitoring.	No new studies were identified	None relevant	All 6 experts thought this conclusion was still valid	The conclusion is still valid

Legend: ACEI=Angiotensin Converting Enzyme Inhibitors; AKI= Acute Kidney Injury; ARB=Angiotensin Receptor Blocker; ARF= Acute Renal Failure; BP=Blood Pressure; CHF=Congestive Heart Failure; CKD=Chronic Kidney Disease; eGFR=Epidermal growth factor receptor; ESRD=End-Stage Renal Disease; FDA=Federal Drug Administration; KDIGO=Kidney Disease: Improving Global Outcomes; MI=Myocardial Infarction; NSAID=Non-steroidal anti-inflammatory drug; RCT=Randomized Controlled Trial; SCEPC=Southern California Evidence-based Practice Center

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Appendices

Appendix A: Search Methodology

Appendix B: Evidence Table

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

Screening (KQ1, KQ2)
Database: Ovid MEDLINE(R)
Update searched 7 August 2012
Search Strategy:
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1. exp mass screening/ or screening.tw. or exp early diagnosis/
2. (expression screening or throughput screening or molecular screening or pharmaceutical screening or mutation screening or genetic screening).tw. or exp genetic screening/ or cancer screening.tw. or compound screening.tw. or drug screening.tw. or exp drug evaluation,preclinical/
3. 1 not 2
4. (randomized controlled trial or controlled clinical trial).pt. or random*.ti,ab. or placebo.ab. or exp Double-Blind Method/
5. exp albuminuria/ or exp proteinuria/ or exp glomerular filtration rate/ or exp creatinine/ or exp kidney function tests/ or exp cystatins/ or exp kidney diseases/ or kidney$.ti. or nephr$.ti. or renal.ti. or exp kidney/
6. 3 and 4 and 5
7. exp animals/ not humans.sh.
8. 6 not 7
9. limit 8 to english language
10. limit 9 to yr= “2011 -Current”
11. limit 10 to “all child (0 to 18 years)”
12. limit 10 to “all adult (19 plus years)”
13. 11 not 12
14. 10 not 13
15. (new england journal of medicine or jama or bmj or lancet or annals of internal medicine or kidney international or american journal of kidney diseases or diabetes care or archives of internal medicine or journal of the american society of nephrology).jn.
16. 14 and 15
Results: 4

Monitoring (KQ3, KQ4)
Database: Ovid MEDLINE(R)
Update searched 7 August 2012
Search Strategy:
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1. monitoring.tw. or exp disease progression/
2. cardiac monitoring.tw. or exp drug monitoring/ or exp environmental monitoring/ or drug monitoring.tw. or exp blood glucose self-monitoring/ or exp blood gas monitoring, transcutaneous/ or exp clinical trials data monitoring committees/ or exp esophageal pH monitoring/ or exp monitoring, immunologic/ or exp uterine monitoring/ or exp monitoring, intraoperative/ or exp radiation monitoring/ or exp monitoring, physiologic/
3. 1 not 2

4. (randomized controlled trial or controlled clinical trial).pt. or random*.ti,ab. or placebo.ab. or exp Double-Blind Method/
5. exp albuminuria/ or exp proteinuria/ or exp glomerular filtration rate/ or exp creatinine/ or exp kidney function tests/ or exp cystatins/ or exp kidney diseases/ or kidney$.ti. or nephr$.ti. or renal.ti. or exp kidney/
6. 3 and 4 and 5
7. exp animals/ not humans.sh.
8. 6 not 7
9. limit 8 to english language
10. limit 9 to yr="2011 -Current"
11. limit 10 to "all child (0 to 18 years)"
12. limit 10 to "all adult (19 plus years)"
13. 11 not 12
14. 10 not 13
15. (new england journal of medicine or jama or bmj or lancet or annals of internal medicine or kidney international or american journal of kidney diseases or diabetes care or archives of internal medicine or journal of the american society of nephrology).jn.
16. 14 and 15

Results: 17

Treatment (KQ5, KQ6)

Database: Ovid MEDLINE(R)
Update searched 7 August 2012
Search Strategy:

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1. exp albuminuria/co, de, dh, dt, mo, pc, th or exp proteinuria/co, de, dh, dt, mo, pc, th or exp glomerular filtration rate/ or exp kidney diseases/co, de, dh, dt, mo, pc, th or exp kidney/co, de, dh, dt, mo, pc, th or exp diabetic nephropathies/co, de, dh, dt, mo, pc, th or exp kidney failure, chronic/co, de, dh, dt, mo, pc, th or exp chronic renal insufficiency/co, de, dh, dt, mo, pc, th or exp renal insufficiency/co, de, dh, dt, mo, pc, th or exp renal insufficiency, chronic/co, de, dh, dt, mo, pc, th
2. exp *renal replacement therapy/ or exp renal dialysis/ or exp *kidney neoplasms/ or *nephritis/ or exp *urinary tract infections/ or exp *urolithiasis/ or exp anuria/ or exp diabetes insipidus/ or exp fanconi syndrome/ or exp hepatorenal syndrome/ or exp hydronephrosis/ or exp kidney cortex necrosis/ or exp Kidney Diseases, Cystic/ or kidney papillary necrosis/ or exp nephritis/ or exp renal artery obstruction/ or exp Renal Tubular Transport, Inborn Errors/ or exp Tuberculosis, Renal/ or exp Zellweger syndrome/ or exp AIDS-Associated Nephropathy/ or exp Hyperoxaluria/ or exp Nephrocalcinosis/ or exp Perinephritis/ or exp Renal Osteodystrophy/
3. 1 not 2
4. (randomized controlled trial or controlled clinical trial).pt. or random*.ti,ab. or placebo.ab. or exp Double-Blind Method/ or randomized controlled trials as topic/
5. 3 and 4
6. exp animals/ not humans.sh.
7. 5 not 6
8. limit 7 to english language
9. limit 8 to yr="2011 -Current"

10. limit 9 to “all child (0 to 18 years)”
11. limit 9 to “all adult (19 plus years)”
12. 10 not 11
13. 9 not 12
14. (new england journal of medicine or jama or bmj or lancet or annals of internal medicine or kidney international or american journal of kidney diseases or diabetes care or archives of internal medicine or journal of the american society of nephrology).jn.
15. 13 and 14
Results: 72
Total after removing duplicates: 81
These articles came up in multiple searches:
mo = monitoring tx = treatment sc = screening

Balasubram: mo/tx
Bhavsar: mo/tx
de Boer: mo/tx
Fink: mo/tx/sc
Mallamaci: mo/tx
Paulson: sc/mo
Sharma: mo/tx
Li: mo/tx
Hirst: mo/tx
Johnson: mo/tx
Rapheal: mo/tx

Appendix B. Evidence Table

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
CKD Treatment Benefits and Harms						
Sharma, 2011[19]	RCT of pirfenidone at 1200 or 2400mg vs placebo	77	Diabetic nephropathy with elevated albuminuria and GFR 20-75 ml/min	Change in GFR after 1 year of therapy	12 months	Among 52 completers, the mean GFR increased in the pirfenidone group (+3.3+/-8.5 ml/min) and decreased in placebo group (-2.2 +/-4.8 ml/min) (P=0.026)
Lewis, 2011[14]	RCT of sulodexide vs placebo	1056	Type 2 diabetes and urine albumin-creatinine ratios (ACR) of 35-200 mg/g (males) and 45-200 mg/g (females)	Normoalbuminuria (ACR <20 mg/g and a decrease >25%) or 50% decrease in baseline ACR	34 weeks	Primary endpoint was achieved in 16.5% with sulodexide vs 18.4% with placebo, normoalbuminuria in 7.9% vs 6.1%, 50% decrease in albuminuria in 15.4% vs 17.6%. The relative probability of any given change in albuminuria was identical in both groups
Pergola, 2011[18]	RCT of bardoxolone methyl at a target dose of 25, 75, or 150 mg qD vs placebo	227	Adults with CKD (GFR 20-45 ml/min/ 1.73 m2 BSA)	Change from baseline in estimated GFR	52 weeks	Patients receiving bardoxolone methyl had significant increases in eGFR compared with placebo at 24 weeks with between-group differences per minute per 1.73 m2 of 8.2+/-1.5 ml in 25mg group, 11.4+/-1.5ml in 75mg group and 10.4=/-1.5 ml in 150mg group (P<0.001). Increases were maintained through week 52 with significant decreases of 5.8+/-1.8ml, 10.5+/-1.8ml, 9.3+/-1.9ml. Adverse effects were more common in bardoxolone group including mild, dose-related muscle spasms, hypomagnesemia, mild increases in alanine aminotransferase levels and GI effects

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Slagman, 2011[20]	RCT of ACE-I and ARB or placebo combined with low sodium (LSD) or regular sodium (RSD)diet	52	Patients with non-diabetic nephropathy	Proteinuria	4, 6 week periods	Geometric mean residual proteinuria was 1.68 (95% CI 1.31-2.14) g/day during ACE-I plus RSD Adding ARB reduced proteinuria to 1.44 (1-07-1.93) g/day (P=0.003), addition of a LSD reduced it to 0.85 (0.66-1.10) g/day (P<0.001) and addition of ARB + LSD reduced it to 0.67 (0.50-0.91) g/day (P<0.001). The reduction of proteinuria by the addition of a LSD (51%, 95% CI 43-58%) was significantly larger (P<0.001) than reduction by addition of ARB (21% CI 8-32%) (P=0.009) comparable to reduction in proteinuria by addition of both ARB and LSD (62%, 53%-70%)
Kohan, 2011[12]	RCT of atrasentan (0.25, 0.75 or 1.75mg) vs placebo in subjects with diabetic nephropathy already receiving stable doses of renin-angiotensin system inhibitors	89	GFR >20 ml/min per 1.73 m2 and urinary albumin-to-creatinine ratio (UACR) of 100-3000 mg/g	Change from baseline in UACR	8 weeks	Atrasentan reduced UACR only in the 0.75 and 1.75mg groups, compared to placebo (P=0.001 and P=0.011). Peripheral edema occurred in 9% of placebo and 14, 18 and 46% of those receiving 0.25, 0.75 and 1.75mg of atrasentan (P=0.007 for 1.75mg vs placebo)
Weir, 2012[23]	RCT of benazepril plus either hydrochlorothiazide or amlodipine, titrated to BP goals	1414	Subset of black patients in ACCOMPLISH trial	Doubling in serum creatinine, ESR or death	3 years	Doubling in serum creatinine, ESRD or death was not different between Black and non-Black patients, although Blacks were significantly more likely to develop a > 50% increase in serum cr to a level above 2.6 mg/dl. benazepril coupled to amlodipine was a more effective antihypertensive treatment than when coupled to hydrochlorothiazide in non-Black patients. Blacks have modestly higher increased risk for more advanced increases in serum Cr than non-Blacks

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Hellemons, 2011[9]	Post-hoc analysis of RCT (IRMA-2 trial) of irbesartan vs plaebo on top of antihypertensive treatment	531	IRMA-2 enrolled hypertensive patients with type 2 diabetes and microalbuminuria	Urinary albumin excretion (UAE) and systolic blood pressure (SBP) and the individual effect of both response parameters on change in eGFR	2 years	In irbesartan treated patients 24.4% had a >median reduction in UAE but not in SBP and 19.3% had a >median reduction in SBP but not UAE. The degree of reduction in UAE was independently associated with the rate of eGFR decline (P=0.0037). SBP showed a similar trend (P=0.087). The more UAE reduction the less eGFR decline, irrespective of SBP change.
Harcourt, 2011[8]	Randomized crossover trial of 2 weeks each on a low and high AGE- containing diet	11	Overweight and obese individuals (BMI 26-39 kg/m2)	Renal function, inflammatory profile (MCP-1) and macrophage migration inhibitory factor (MIF)	4 weeks	Urinary albumin/ creatinine ratios were significantly better following the low AGE dietary period in obese individuals (low v high AGE diet: P=0.02). MCP-1 was increased with high AGE diet (low vs high: P=0.04). MIF declined with high AGE (low vs high: P=0.04)
Holtkamp, 2011[11]	Post-hoc analysis of RCT (RENAAL trial) of losartan vs plaebo	1435	Non-insulin dependent diabetes	Change in GFR	39 months	Patients assigned to losartan had a significantly greater acute fall in eGFR during the first 3 months, compared to placebo, but significantly slower long-term mean decline of eGFR thereafter. Patients with a large initial fall in eGFR had a significantly lower long-term eGFR slope compared to those with a moderate fall or rise. Thus, the greater the acute fall in eGFR during losartan treatment, the slower the rate of long-term eGFR decline.
Broedbaek, 2011[6]	Substudy of IRMA-2 trial of irbesartan vs plaebo on top of antihypertensive treatment	50	Hypertensive type 2 diabetic patients with microalbuminuria for which urine specimens were available	Changes in albumin and nucleic acid excretion	24 months	No significant differences in nucleic acid excretion (8-oxodG and 8-oxoGuo) between placebo and irbesartan treatment. 8-oxodG and albumin excretion decreased with time (P=0.0004 and P<0.0001), whereas treatment-related differences were shown for albumin excretion (P=0.0008) only. 8-oxodG excretion decreased by 3% in smokers and 26% in nonsmokers (P=0.015), and urinary albumin excretion decreased 22% in smokers and 58% in nonsmokers (P=0.011)

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Melamed, 2011[15]	RCT of raloxifene 60 or 120mg vs placebo	7705	Post-menopausal women with osteoporosis	Changes in serum creatinine	3 years	Those on raloxifene had slower yearly rate of increase in creatinine (significant at the low dose) than those on placebo and a significantly slower yearly rate of decrease in eGFR for both doses. Raloxifene was associated with significantly fewer kidney-related adverse events compared with placebo.
Packham, 2012[17]	RCT of ARB + sulodexide vs ARB+placebo Sun-MACRO trial	1248	Type 2 diabetes, renal impairment and significant proteinuria	Composite of doubling of baseline serum creatinine, development of ESRD or serum creatinine >6.0 mg/dl	10.7-11.2 months	No significant differences between sulodexide and placebo. The primary composite end point occurred in 26 patients in the sulodexide group and 30 patients in the placebo group. Side effects were similar
Lewis, 2012[13]	RCT of Pyridorin 150mg, 300mg or placebo, BID	317	Proteinuric type 2 diabetic nephropathy	Statistically significant change in serum creatinine (Cr)	52 weeks	Among patients in lowest tertile of baseline serum Cr, treatment with Pyridorin associated iwth a lower average change in serum Cr at 52 weeks (0.28 placebo, 0.07 Pyridorin 150mg, 0.14 Pyridorin 300mg (P=0.05). There was no evidence of significant treatment effect in the middle or upper tertiles
Goraya, 2012[7]	Case series of ACEI +alkali-inducing fruits and vegetables OR oral sodium bicarb OR no intervention	27	Hypertensive nephropathy at stage 1 or 2 eGFR	Indices of kidney injury	30 days	Indices of kidney injury were not changed in Stage 1 patients. However, stage 2 patients decreased urinary albumin, N-acetyl B-D-glucosaminidase and transforming growth factor B from the controls to a similar extent. Reducing dietary acid decreased kidney injury and using fruits and vegetables was comparable to sodium bicarbonate.
Tangri, 2011[21]	Post-hoc analysis of data in the Modification of Diet in Renal Disease study	741	Patients with CKD stages 3 and 4	Relationship between dietary protein intake and creatinine and cystatin C levels	2 years	Lowering the dietary protein intake reduced the change in creatinine but did not have a significant change in cystatin C
CKD Monitoring Benefits and Harms						

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Bhavsar, 2011[5]	RCT followed by observational cohort study, comparing ability of mGFR, serum Cr, eGFRscr, cystatin C level and BTP level to predict ESRD and mortality	865	African Americans with hypertensive CKD enrolled in AASK	Utility of markers of kidney function to predict incidence of ESRD and mortality	102 months (median)	Plasma BTP and cystatin C levels may be useful adjuncts to serum creatinine level and mGFR in evaluating risk of progression of kidney disease
Abdel-Kader, 2011[4]	Cluster-RCT of educational sessions and automated alerts for PCPs caring for patients with CKD	30	PCPs in university-based outpatient internal medicine clinic and their 248 patients with moderate to advanced CKD	Referral to a nephrologist	10 months	Intervention and control did not differ in renal referrals (9.7% vs 16.5%; between group difference -6.8%; 95% CI -15.5%-1.8%; P=0.1) or proteinuria assessments (39.3% vs 30.1%, between-group difference, 9.2%; 95% CI -2.7-21.1%; P=0.1)
Methven, 2010[16]	Retrospective longitudinal cohort study of urinary albumin and urinary total protein to predict patient outcomes	5586	CKD and proteinuria	All-cause mortality, start of renal replacement therapy (RRT), doubling of serum creatinine level	3.5 years median	Adjusted HRs were similar for total protein-creatinine ratio and albumin-creatinine ratio for all outcomes: death 1.41 (95% CI, 1.31-1.53) vs 1.38 (95% CI, 1.28-1.50), RRT 1.96 (95%CI, 1.76-2.18) vs 2.33 (95%CI, 2.06-3.01) and doubling serum creatinine level 2.03 (95% CI, 1.87-2.19(vs 1.92 (95%CI, 1.78-2.08)
Weiner, 2009[22]	Cohort of participants in the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study	20,993	People in those studies with at least 2 GFR measurements	Whether one vs two eGFR assessments changes the prognosis	35.3+/-2.5 months	Individuals with persistentl reduced eGFR are at the highest risk of cardiovascular outcomes and mortality while individuals with an eGFR <60 mL/min per 1.73 m2 at any time are at intermediate risk.

Author, year	Trial	n	Subjects	Primary Outcome	Duration	Findings
Hemmelgarn, 2010 [10]	Community-based cohort study of GFR, proteinuria and adverse clinical outcomes	920,985	At least 1 outpatient serum creatinine measurement	All-cause mortality, myocardial infarction, progression to kidney failure	35 months (0-59 months)	3% died, with the fully adjusted rate of all-cause mortality higher in study participants with lower eGFRs, 2 fold higher with heavy proteinura and eGFR >60ml/min/1.73m2 vs eGR 45-59.9mL/min/1.73m2 and normal protein excretion (rate, 7.2[95% CI 6.6-7.8] vs 2.9 [95% CI 2.7-3.0] per 1000 person-years, respectively; rate ratio, 2.5 [95% CI, 2.3-2.7]. Similar results for proteinuria measured by ACR (15.9[95% CI 14.0-18.1- heavy proteinuria] and 7.0 {95% CI 6.4-7.6- absent proteinuria), rate ratio 2.3 [95%Ci 2.0-2.6] and for outcomes of hospitalization with acute MI, ESRD and doubling of serum creatinine

Legend: ACEI=Angiotensin Converting Enzyme Inhibitors; AKI= Acute Kidney Injury; ARB=Angiotensin Receptor Blocker; ARF= Acute Renal Failure; BMI=Body Mass Index; BP=Blood Pressure; BTP=Beta-trace protein; CHF=Congestive Heart Failure; CKD=Chronic Kidney Disease; eGFR=Epidermal growth factor receptor; ESRD=End-Stage Renal Disease; FDA=Federal Drug Administration; KDIGO=Kidney Disease: Improving Global Outcomes; LSD=Low Sodium Diet; MI=Myocardial Infarction; MIF=Migration Inhibitory Factor; NSAID=Non-steroidal anti-inflammatory drug; RCT=Randomized Controlled Trial; RSD=Regular Sodium Diet; SBP=Systolic Blood Pressure; SCEPC=Southern California Evidence-based Practice Center; UAE=Urinary Albumin Excetion

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: **Chronic Kidney Disease Stages 1–3: Screening, Monitoring, and Treatment**

Name of Person Completing the Form: _____

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
CKD Treatment Benefits and Harms			
In RCTs of patients with CKD Stages 1-3 several treatments reduced the risk of clinical outcomes, but the benefits appeared to be limited to specific CKD subgroups, some of which already had a clinical indication for the treatment studied (Table A).	☐	New Evidence:	☐
ACEI and/or ARB treatment significantly reduced ESRD risk in patients with proteinuria (macroalbuminuria), most of whom had diabetes and hypertension. ESRD was not significantly reduced in patients with CKD stages 1–3 who did not have proteinuria. Patients with proteinuria, diabetes, and hypertension may benefit from ACEI or ARB treatment.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
ACEI treatment significantly reduced mortality risk in patients known to have microalbuminuria who had either cardiovascular disease or the combination of diabetes and other cardiovascular risk factors. Relative risk reduction was not significantly different than in similar patients who did not have microalbuminuria. Patients who had microalbuminuria and were at high risk for cardiovascular complications may benefit from ACEI treatment at adequate doses.	☐	New Evidence:	☐
Statins significantly reduced the risk of mortality, myocardial infarction (MI), and stroke in patients with hyperlipidemia and impaired eGFR or creatinine clearance, including those without coronary artery disease. Patients with hyperlipidemia and no coronary artery disease may not otherwise have an indication for statins, but the subset with CKD may benefit from treatment. No statin trials reported clinical outcomes data for patients with albuminuria.	☐	New Evidence:	☐
Beta blockers significantly reduced the risk of mortality, MI, and congestive heart failure (CHF) events in patients with CHF and impaired eGFR, most of whom already were treated with an ACEI or ARB. Patients with systolic CHF already have an indication for beta blockers, regardless of whether they have CKD.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
In RCTs that compared different active treatments head to head (e.g., ACEI versus ARB, ACEI versus beta blocker), there was no consistent significant difference in clinical outcomes between treatments, with strength of evidence ranging between low and insufficient for different comparisons.	☐	New Evidence:	☐
In RCTs that compared high- versus low-dose treatment (ARB, statin), strict versus standard control (blood pressure, glycemia), combination versus monotherapy, and intensive multidisciplinary interventions (simultaneous targeting of blood pressure, diabetes, cholesterol, and/or reducing nephrotoxic drug exposure) versus usual care, there was no consistent significant difference in clinical outcomes between treatments, with strength of evidence ranging between low and insufficient for different comparisons.	☐	New Evidence:	☐
Low-protein diets did not significantly reduce risk of mortality, ESRD, or any clinical vascular outcome compared with usual protein diets; risk for a composite renal outcome was significantly reduced in one trial, but this study also included participants with CKD stages 4–5.	☐	New Evidence:	☐
Although limitations in reporting impeded the quantitative synthesis of withdrawal and adverse events data from different studies, adverse events reported generally were consistent with known potential adverse effects of these treatments (e.g.,	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
hypotension with antihypertensives; cough with ACEIs; edema with calcium channel blockers; hyperkalemia with ACEIs, ARBs, and aldosterone).			
CKD Screening Benefits and Harms			
We found no direct RCT evidence that addressed whether systematic screening of adults for CKD improves clinical outcomes or increases harms.	☐	New Evidence:	☐
Results from studies not directly linking systematic CKD screening to clinical outcomes contributed indirect evidence regarding whether CKD screening improves clinical outcomes.	☐	New Evidence:	☐
Microalbuminuria and eGFR are sensitive screening tests for detecting one-time kidney abnormalities that may reflect CKD, but false positive rates are substantial, particularly for microalbuminuria; their sensitivity and specificity for CKD as defined by kidney dysfunction or damage lasting 3 months or longer is unknown.	☐	New Evidence:	☐
Most patients with CKD stages 1–3 are clinically unrecognized. Because even populations with a high CKD prevalence (e.g., diabetes, hypertension, cardiovascular disease, older age) are not routinely tested for CKD, especially for albuminuria, systematic screening likely would lead to a large increase in CKD	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
diagnoses.			
Because of the above-noted treatment benefits in patients who have cardiovascular disease or diabetes combined with other cardiovascular risk factors (e.g., hypertension) and are known to have albuminuria, screening such patients for microalbuminuria or macroalbuminuria could lead to early initiation of ACEI or ARB treatment and reduced risk of mortality or ESRD.	☐	New Evidence:	☐
Because of the above-noted treatment benefits in patients who have hyperlipidemia without cardiovascular disease and are known to have impaired eGFR or creatinine clearance, screening such patients for impaired eGFR could lead to early initiation of statin treatment and reduced risk of mortality, MI, or stroke.	☐	New Evidence:	☐
Virtually no RCTs of CKD treatments identified participants through screening, so the generalizability of treatment RCT results to patients with CKD stages 1–3 identified through screening is unknown.	☐	New Evidence:	☐
We found insufficient strength of evidence addressing potential harms associated with systematic CKD screening.	☐	New Evidence:	☐
CKD Monitoring Benefits and Harms			

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
We found no direct RCT evidence regarding whether systematic monitoring of adults with CKD stages 1–3 for worsening kidney function or damage improves clinical outcomes.	☐	New Evidence:	☐
Results from studies not directly linking systematic CKD monitoring to clinical outcomes contributed indirect evidence regarding whether CKD monitoring improves clinical outcomes.	☐	New Evidence:	☐
Because of the above-noted treatment benefits in patients with albuminuria who have cardiovascular disease or have diabetes combined with other cardiovascular risk factors (e.g., hypertension), monitoring patients with impaired eGFR for development of albuminuria could lead to early initiation of ACEI or ARB treatment and reduced mortality or ESRD risk.	☐	New Evidence:	☐
Because of the above-noted treatment benefits in patients with hyperlipidemia who have impaired eGFR or creatinine clearance, monitoring such patients for development of impaired eGFR could lead to early initiation of statin treatment and reduced risk of mortality, MI, or stroke.	☐	New Evidence:	☐
In patients with CKD stages 1–3, kidney function usually slowly worsens over years, but may worsen faster in selected subgroups (e.g., those with diabetes,	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
proteinuria, hypertension, older age, obesity, or dyslipidemia).			
The sensitivity and specificity of eGFR and albuminuria for identifying CKD progression in patients with CKD stages 1–3 are unknown.	☐	New Evidence:	☐
The vast majority of patients with recognized CKD stages 1–3 have serum creatinine measured regularly, so implementation of systematic eGFR monitoring may have only a limited impact on current practice. Because only a minority of patients with CKD stages 1–3 are annually tested for albuminuria, systematic albuminuria monitoring likely would lead to an increase in patients identified with clinical worsening of CKD.	☐	New Evidence:	☐
We found insufficient strength of evidence addressing potential harms associated with systematic CKD monitoring.	☐	New Evidence:	☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			